REMARKS

Amendments

Claim 1 is amended to incorporate the features recited in claim 16. Thus, claim 1 now corresponds to claim 16 written in independent form. Claims 2-22, 24-25, 34-39 are cancelled. Claim 1 is also amended to recite prodrug derivatives. See, e.g., page 10, lines 18-25. Claims 23 and 42 are amended to be consistent with the amended language of claim 1. Claims 26 is amended to be consistent with the amended language of claim 1 and to delete superfluous language. Claim 29, 40 and 41 are amended to correct obvious spelling errors.

New claims 43-60 are directed to further aspects of applicants' invention and are supported throughout the disclosure. See, e.g., page 13, lines 5-14, page 15, line 1, page 20, lines 6-12, page 20, lines 33-34, and page 21, line 5.

Restriction

Reconsideration of the Restriction is again respectfully requested. In response to applicants' arguments that unity of invention exists based on Annex B, section (e) of the Administration Instructions Under the PCT, the Examiner aserts that the only commonality is a carbonyl group (this assertion is no longer correct in view of the amendments to claim 1). However, the assertion that a carbonyl group is the only commonality does not address the rationale presented in Annex B, section (e).

Annex B, section (e) of the Administrative Instructions Under the PCT, clearly states that there **special groups of categories of claims that are considered as satisfying the requirement of unity of invention**. One of these groups is where there is an independent claim directed to product, and independent claim directed to a process for manufacturing the product, and an independent claim directed to a use of the product. This is the situation presented by the instant group of claims. Asserting that the compounds of Group I have a carbonyl group as the only commonality does not refute the fact that the claims of Groups I-III are directed to a special category of claims that Annex B, section (e) states will be considered as satisfying the requirement of unity of invention.

In view of the above remarks, it is respectfully submitted that there is no basis under PCT Rule 13.1 for Restriction of the claims of Groups II and III from the claims of Group I.

Withdrawal of the Restriction is again respectfully requested.

Elected Species Not Rejected in view of Prior Art

In the May 28, 2008 Office Action, it is stated that the elected compound was not allowable. However, the issue regarding examination in accordance with MPEP §803.2 is whether the elected species of the Markush claim is found to be anticipated or obvious by prior art. In the instant case, the Office Action does not demonstrate that the elected species of 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide is anticipated or obvious in view of prior art. In fact, the only prior art rejection presented in the Office Action did not reject claim 16, which encompasses the elected species.

Thus, examination should proceed in accordance with MPEP §803.2. Clarification as to the scope of examination is requested.

Rejection under 35 USC 112, first paragraph

Claims 1-20, 22, 23, 29, and 30 are rejected under 35 USC 112, first paragraph, as allegedly lacking enablement with respect to solvates. This rejection is respectfully traversed.

Referring to the Wands factors, the Examiner argues that the claims encompass solvates, that preparing polymorphs is unpredictable, that its not commonly know how different solid forms are made, and that there are no working examples of solvates. It is noted that the claims refer to solvates, not polymorphs. Thus, arguments regarding polymorphs are not relevant to the present issue.

With respect to the so-called Wands factors, these factors are used to determine whether undue experimentation is involved. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). However, before the issue of undue experimentation arises, the PTO must present reasons to doubt the veracity of the objective enablement statements presented in an applicants' specification.

In making a lack of enablement rejection, it is the initial burden of the PTO to establish a reason to doubt the truth of the statements presented in the specification concerning enablement. See, e.g., *In re Marzocchi et al.,* 169 USPQ 367, 370 (CCPA 1971). It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain

why it doubts the truth or accuracy of any statement in a supporting disclosure. In addition, as stated in the *Marzocchi* decision:

> "a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support" (emphasis in original).

See *In re Marzocchi*, at 369. See also *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995). Thus, all that is required under the statute is **objective** enablement.

The specification combined with knowledge within the art provides more that sufficient guidance to objectively enable one of ordinary skill in the art to make and use the claimed compounds. The formation of solvates is well known within the art. Combining a solvent with a compound to produce of a solvate requires no more than routine experimentation. That which is well known in the art need not be presented in the specification. See, e.g., *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986)

The rejection presents no rationale as to why one of ordinary skill in the art would doubt the objective enablement provided by applicants' disclosure and the state of the art. A considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction the experimentation should proceed. *In re Wright,* 999 F.2d 1557, 1561 (Fed. Cir, 1993).

In discussing the Wands factors, the Examiner argues that formation of polymorphs is unpredictable. While this assertion is not relevant to the issue of solvate formation, still even if an art is alleged to be unpredictable this does not establish non-enablement. See, e.g., *In re Angstadt*, 190 USPQ 214, 219 (CCPA 1976) in which the art involved (catalysis) was acknowledged to be unpredictable, yet the court still found the disclosure in question to be enabling.

The rejection also asserts that working examples of solvates are not provided.

Examples are not required under the statute. See, for example, the decision in *Marzocchi* wherein the Court expressly stated that:

> The only relevant concern of the Patent and Trademark Office under the circumstances should be over the *truth* of the assertion. The first paragraph of §112 requires nothing more than objective enablement. **How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.** (emphasis added) (*Marzocchi* at 369)

See also MPEP § 2164.02 which acknowledges that compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed.

One of ordinary skill in the art in the field of pharmaceuticals would know how to proceed in preparing solvates and how such solvates can be identified or characterized, e.g., by polarized light microscopy, etc. Additionally, one of ordinary skill in the art would also have a good expectation for success. While certain predictions may be difficult in the art of forming solvates, the formation of solvates is common with pharmaceutically active ingredients and methods of detecting and characterizing them are well-known and widely applied routinely.

While the amount of work to prepare solvates of the compounds of the invention may require some effort or maybe even considerable effort (although not admitted), no undue experimentation is required in the preparation of solvates. "The test of enablement is whether one reasonably skilled in the art could make or use the invention from disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics*, 8 USPQ2d 1217 (Fed. Cir. 1988). One of ordinary skill in the art merely through routine laboratory efforts can take the finite number of compounds of the claimed invention, bring them together with various solvents, i.e., water or various alcohols in the present case, and check whether a solvate has formed. This type of work is merely routine laboratory work and does not require undue experimentation. Moreover, as discussed in *Wands*, the "test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine," which it is in the present case.

Enclosed is copy of the article, *Vippagunta et al.*, "Crystalline Solids," Abstract Drug Delivery Reviews, 48 (2001), 3-26. While *Vippagunta* does indicate that certain predictions

about solvates or hydrates of a compound may be complex or difficult, the article discloses that solvates are well known. For example, *Vippagunta* on page 15, top of first column, states that

> It has been established that approximately one-third of the pharmaceutically active substances are capable of forming crystalline hydrates. (Emphasis added.)

Likewise, the abstract of *Vippagunta* starts with the statement that

> Many drugs exist in the crystalline solid state due to reasons of stability and ease of handling ... Crystalline solids can exist in the form of polymorphs, solvates or hydrates. (Emphasis added.)

Also on page 4, first paragraph, *Vippagunta* states that

> Most organic and inorganic compounds of pharmaceutical relevance can exist in one or more crystalline forms. ...
>
> The common crystalline forms found for a given drug substance are polymorphs and solvates. (Emphasis added.)

Moreover, *Vippagunta* throughout the reference teaches various solvates, hydrates, etc., structural aspects thereof, examples thereof, including preparation techniques, and methods/techniques for the characterization thereof. See, e.g., pages 15-18.

While it may be true that the prediction of what a particular solvate of a compound will actually look like, e.g., whether 1, 2 or 3 ½, etc. solvent molecules are incorporated, the Office Action is incorrect with respect to the alleged lack of enablement.

Vippagunta demonstrates that one of ordinary skill in the art in the field of pharmaceuticals would know how to proceed in preparing solvates, and how such solvates would be identified or characterized, e.g., by polarized light microscopy, etc. See extensive list of techniques identified on column 2 of page 18.

Additionally, based on the above discussed statistics in this field provided by *Vippagunta*, one of ordinary skill in the art would also have a good expectation for success. While certain predictions may be difficult in the art of forming solvates, the formation of solvates is common and routine for pharmaceutically active ingredients and methods of detecting and characterizing them are well-known and widely applied routinely.

Applicants provide further information clearly demonstrating that solvate formation is

a common phenomenon among pharmaceutical substances, i.e., Polymorphism: in the pharmaceutical industry (edited by *Ralf Hilfiker*; 2006 Wiley-VCH), Chapter 8, The Importance of Solvates, by *U. J. Griesser*, pp. 211-222 (hereinafter *Griesser*).

On page 220, *Griesser* teaches that

> Over almost two decades we carefully collected data on the solid-state properties of a few thousand pharmaceutically relevant organic compounds, with special focus on those drug substances listed in the Pharmacopoeia European (PhEur). The 1997 edition of PhEur contained 559 well-defined organic drug compounds. ... For more than 55% of them either polymorphs or solvates are known. In a newer evaluation of a larger set of data (PhEur edition 4.02, 8008 solid organic compounds ... this fraction increased only slightly to 57%. As shown in Fig. 8.4, 29% of the compounds are known to form hydrates, 10% other solvates ... (Emphasis added.)

Additionally, various factors in considering whether solvates would be expected to form are identified by *Griesser* on pages 220-221, e.g., salt forms, molecular size, lipophilicity. A citation is provided for ascertaining "further trends and interrelations between molecular properties and solvate/hydrate formation." See the middle of page 221. All this demonstrates that one of ordinary skill in the art would know or have guidance as to what factors to consider in expectation of success.

Moreover, under the section titled "Generation and Characterization of Solvates" on page 222, *Griesser* teaches that

> Since it is imperative to establish the crystal forms of an active pharmaceutical ingredient (API) to satisfy the regulatory authorities ..., solvates of drug compounds are now preferentially discovered in systematic polymorph screenings. ... **Automated crystallization systems and strategies** have been developed to speed up this process, **allowing thousands of crystallization experiments in a short time**. (Emphasis added.)

Thus, the Office Action has not carried its burden in establishing a lack of enablement because the Office Action has not established any basis to doubt objective enablement. See the holding in *Marzocchi* at page 369 that a specification disclosure which "contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be

patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." (Emphasis added.) See also *In re Bundy*, 209 USPQ 48 (1981) holding that the "PTO must have adequate support for its challenge to the credibility of applicant's statements of utility," which statements were made in *Bundy* in the context of an enablement rejection, and which is lacking in the present case.

In view of the state of the art, it is evident that there is no indication that one of ordinary skill in the art would have questioned that solvates could be formed. See *Rasmusson v. Smithkline Beecham Co.*, 75 USPQ2d 1297 (CA FC 2005). As such, there is no basis for the rejection. Nothing in the record of the present case provides basis for doubt, and the USTPO has not provided any evidence substantiating any such doubts. No relevant statements in the application are contrary to generally accepted scientific principles on their face.

In view of the state of the art of solvate formation, e.g., solvate formation being a very common phenomenon associated with drug substances, the generation and examination of which is done with highly automated machines, the Office Action has not established that it would require undue experimentation by one of ordinary skill in the art to prepare and even characterize solvates of a specific compound of the present claims.

In view of the above remarks, it is respectfully enabled that the claims reciting solvates are sufficiently enabled in light of applicants' disclosure and the knowledge within the art. Withdrawal of the rejection is requested.

Rejection under 35 USC 112, second paragraph

Claims 1-20, 22, 23, 29, and 30 are rejected under 35 USC 112, first paragraph, as allegedly being indefinite with respect to the term derivatives. This rejection is respectfully traversed.

As acknowledged in the rejection, the term "derivative" has an art recognized definition. Since the term is well known in the art, one of ordinary skill in the art would find the term to be definite.

In addition, the claims are amended to recite "prodrug derivatives." This term is

expressly defined in applicants' specification. See, e.g., page 10, lines 18-25.

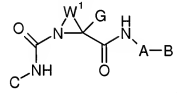
In view of the above remarks, withdrawal of the rejection is respectfully requested.

Rejection under 35 USC 102(e)

Claims 1-15, 17, 19, 29, 30, and 32 are rejected under 35 USC 102(e) as allegedly being anticipated in view of the disclosure of Bigge et al. (US 2003/0162787). This rejection is respectfully traversed.

It is noted that this rejection is not applied against claim 16. As claim 1 now corresponds to prior claim 16, it is evident that Bigge et al. does not anticipate or render obvious the instant claims.

Bigge et al. disclose compounds of the following formula:



The compounds of this genus do not anticipate or render obvious applicants' claimed compounds. For example, compare group C of Bigge et al. (see, e.g., paragraph [0011]) and group T of applicants' claim 1.

In view of the above remarks, withdrawal of the rejection is respectfully requested.

Obviousness-type Double Patenting Rejection

Claims 1-20, 22, 23, 29, and 30 are provisionally rejected as allegedly being obvious in view of claims 40-49 of Serial No. 11/575,711. This rejection is respectfully traversed.

The PCT application from which Serial No. 11/575,711 is derived was filed August 24, 2005, well after the filing of the PCT application from which the instant application is derived. Furthermore, an Office Action on the merits has yet to be issued in Serial No. 11/575,711. Thus, it is unclear what will be the final scope of the claims of Serial No. 11/575,711.

In light of these circumstances, and the fact that this is the only art rejection (albeit it not prior art rejection) applied against the instant application, withdrawal of the rejection is respectfully requested so that the instant application can proceed to issue. The question of obviousness-type double patenting can be addressed, if necessary, in the prosecution of Serial

No. 11/575,711.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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